

BERISH RUBIN ET AL.  
USSN 10/050,189  
PRELIMINARY AMENDMENT OF November 14, 2003

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) A method for detecting the presence in a subject of a polymorphism linked to a gene associated with familial dysautonomia, said method comprising detecting a disruptive mutation in a gene of said subject encoding the I $\kappa$ B kinase-complex-associated protein.
2. (Original) The method according to claim 1, which comprises detecting a disruptive mutation in the gene encoding the I $\kappa$ B kinase-complex-associated protein which is present on chromosome 9q31.
3. (Original) The method according to claim 2, which comprises detecting a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20 of the gene encoding the I $\kappa$ B kinase-complex-associated protein which is present on chromosome 9q31.
4. (Original) The method according to claim 2, which comprises detecting a G  $\rightarrow$  C transversion of nucleotide 2390 in exon 19 of the gene encoding the I $\kappa$ B kinase-complex-associated protein which is present on chromosome 9q31.
5. (Original) The method according to claim 3 or 4, which comprises detecting

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said T → C change and/or said G → C transversion by single-strand conformational polymorphism (SSCP) analysis.

6. (Original) The method according to claim 5, wherein said SSCP analysis is carried out on a nucleic acid sequence amplified by polymerase chain reaction (PCR).
7. (Original) The method according to claim 6, wherein said nucleic acid sequence is amplified by PCR using one or more oligonucleotide primers selected from the group consisting of:
  - a) GAGAACAACAAGATTCTGC (SEQ ID NO: 6);
  - b) AGTCGCAAACAGTACAATGG (SEQ ID NO: 7);
  - c) GCAGTTAATGGAGAGTGGCT (SEQ ID NO: 8); and
  - d) ATGCTTGGTACTTGGCTG (SEQ ID NO: 9).
8. (Original) An oligonucleotide primer selected from the group consisting of:
  - a) GAGAACAACAAGATTCTGC (SEQ ID NO: 6);
  - b) AGTCGCAAACAGTACAATGG (SEQ ID NO: 7);
  - c) GCAGTTAATGGAGAGTGGCT (SEQ ID NO: 8); and
  - d) ATGCTTGGTACTTGGCTG (SEQ ID NO: 9).

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9. (New) An isolated and purified nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:
- a) a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a major familial dysautonomia haplotype mutation, which is a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20;
  - b) a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a minor familial dysautonomia haplotype mutation, which is a G  $\rightarrow$  C transversion of nucleotide 2390 in exon 19; and
  - c) a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20 and by a G  $\rightarrow$  C transversion of nucleotide 2390 in exon 19.
10. (New) The isolated and purified nucleic acid molecule according to claim 9, comprising the nucleic acid sequence of a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20.

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11. (New) The isolated and purified nucleic acid molecule according to claim 9, comprising the nucleic acid sequence of a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a G  $\rightarrow$  C transversion of nucleotide 2390 in exon 19.
12. (New) The isolated and purified nucleic acid molecule according to claim 9, comprising the nucleic acid sequence of a gene encoding the I $\kappa$ B kinase-complex-associated protein present on chromosome 9q31, said gene being mutated by a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20 and by a G  $\rightarrow$  C transversion of nucleotide 2390 in exon 19.
13. (New) A kit comprising an oligonucleotide primer according to claim 8.
14. (New) A method of detecting a mutation associated with familial dysautonomia, comprising isolated of RNA, amplifying the RNA using a primer flanking said mutation, and determining the presence of a mutated RNA associated with familial dysautonomia, wherein said mutation is selected from the group consisting of:
  - a) a major familial dysautonomia haplotype mutation, which is a T  $\rightarrow$  C change in position 6 of the donor splice site of intron 20;

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- b) a minor familial dysautonomia haplotype mutation, which is a G → C transversion of nucleotide 2390 in exon 19; and
  - c) a combination of a T → C change in position 6 of the donor splice site of intron 20 and a G → C transversion of nucleotide 2390 in exon 19.
15. (New) The method according to claim 14, wherein the mutation is a major familial dysautonomia haplotype mutation, which is a T → C change in position 6 of the donor splice site of intron 20.
16. (New) The method according to claim 14, wherein the mutation is a minor familial dysautonomia haplotype mutation, which is a G → C transversion of nucleotide 2390 in exon 19.
17. (New) The method according to claim 14, wherein the mutation is a combination of a T → C change in position 6 of the donor splice site of intron 20 and a G → C transversion of nucleotide 2390 in exon 19.